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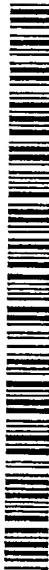
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(54) Title: USE OF MELAGATRAN FOR MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF ISCHEMIC DISORDERS

(57) Abstract: According to the invention there is provided the use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the manufacture of a medicament for the treatment of ischemic disorders in patients having, or at risk of, non-valvular atrial fibrillation.

USE OF MELAGATRAN FOR MANUFACTURE OF A MEDICAMENT FOR THE
TREATMENT OF ISCHEMIC DISORDERS

This invention relates to a new use of the low molecular weight thrombin
5 inhibitor, melagatran and derivatives thereof.

Atrial fibrillation (AF) is characterised by grossly disorganised atrial
electrical activity that is irregular in respect of both rate and rhythm.
Patients with AF have no visually discernible timing pattern in atrial
10 electrical activity when measured by surface ECG, or in electrogram
sequences recorded by catheter electrodes.

During AF, the regular pumping action of the atria is replaced by
irregular, disorganised and quivering spasms of atrial tissue. These
15 spasms may be experienced as irregular heartbeat, palpitations,
discomfort, dizziness and/or angina pectoris. Further, the inefficient
pumping action of the heart tends to lead to significant morbidity related to
reduced blood flow. More seriously, the reduced cardiac output can lead
to blood pooling in the left atria and the formation of blood clots. Blood
20 clots, mostly originating in the left atrium, can dislodge as an embolism
and travel through the bloodstream to organs, e.g. the brain, spleen,
kidneys etc. If the embolism travels to the brain, this may result in
cerebral stroke and even death.

25 In the US alone, AF affects an estimated two million people, with
approximately 160,000 new cases being diagnosed each year. It has been
estimated that AF is responsible for over 70,000 strokes each year in the
US, and that the cost of treating these patients is more than US\$3.6 billion

annually. The cost of drug treatment for AF alone has been estimated to be in excess of US\$400 million world-wide each year.

AF can be classified in two broadly defined groups: "valvular" AF and
5 "non-valvular" AF (NVAF). In valvular AF, the arrhythmia is experienced due to a disorder of one or more of the heart valves (e.g. valvular disease), or the presence of mechanical (prosthetic) heart valves. Conversely, NVAF is AF experienced in the case where there is an absence of significant valvular disease or prosthesis.

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Current drug therapies for AF include antiarrhythmic drugs, administered with a view to re-establishing a normal heartbeat, and anticoagulant and/or thrombolytic drugs, administered with a view to preventing thromboembolism and/or cerebral stroke.

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However, it is estimated that only 40% of patients with AF who should benefit from anticoagulant therapy do so, owing to the risks associated with existing treatments. This also includes patients whose anticoagulant therapy is in combination with cardioversion (electrical or chemical). In
20 particular, of the currently-available oral anticoagulants, warfarin (a vitamin K antagonist) carries the risk of bleeding, and the need for frequent laboratory control. Vitamin K antagonists also demonstrate a notable risk of interaction with other drugs and certain foods, e.g. those that are rich in Vitamin K, and their use requires monitoring of the
25 patient's blood coagulation status. Medication containing acetylsalicylic acid (an antiplatelet agent) also carries the risk of bleeding.

Thus, there is a need for alternative and/or better anticoagulant treatments for use in patients with, or at risk of, AF, and especially NVAF.

International patent application WO 94/29336 discloses a group of compounds that are useful as inhibitors of serine proteases, such as thrombin and/or kininogenases. The thrombin-inhibiting compounds are thus indicated as anticoagulants, and the kininogenase-inhibiting compounds as antiinflammatory agents.

One of the thrombin-inhibiting compounds that is specifically disclosed in WO 94/29336 is HOOC-CH₂-(R)Cgl-Aze-Pab-H, which is also known as melagatran (see Example 1 of WO 94/29336, and the list of abbreviations in that document). International Patent Application WO 97/23499 discloses prodrugs of *inter alia* melagatran.

The use of melagatran and derivatives (including prodrugs) thereof in the treatment of thromboembolic events in patients with NVAF is not disclosed anywhere in the prior art.

We have now found that melagatran and derivatives thereof may be used in the treatment of thrombosis and/or thromboembolic events in patients with NVAF.

According to a first aspect of the invention there is provided the use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the manufacture of a medicament for the treatment of an ischemic disorder, in a patient having, or at risk of, NVAF.

By patient "at risk of" NVAF, we include patients who are in danger of relapsing into NVAF.

For the avoidance of doubt, as used herein, the term "treatment" includes the therapeutic and/or prophylactic treatment of ischemic disorders.

"Pharmaceutically-acceptable derivatives" of melagatran include salts (e.g. pharmaceutically-acceptable non-toxic organic or inorganic acid addition salts) and solvates. It will be appreciated that the term further includes derivatives that have the same biological function and/or activity as melagatran. Moreover, for the purposes of this invention, the term also includes prodrugs of melagatran. The term "prodrug" includes any composition of matter that, following oral or parenteral administration, is metabolised *in vivo* to form melagatran in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration. Prodrugs of melagatran that may be mentioned include those disclosed generically and specifically in international patent application WO 97/23499. Preferred prodrugs are those of the formula $R^1O_2C-CH_2-(R)Cgl-Aze-Pab-OH$ (see the list of abbreviations in WO 97/23499), wherein R^1 represents C_{1-10} alkyl or benzyl, such as linear or branched C_{1-6} alkyl (e.g. C_{1-4} alkyl, especially methyl, *n*-propyl, *i*-propyl, *t*-butyl and, particularly, ethyl) and the OH group replaces one of the amidino hydrogens in Pab.

The term "ischemic disorders" will be understood by those skilled in the art to include any condition, the results of which include a restriction in blood flow in a part of the body. In this context, the term will also be understood to include thrombosis and hypercoagulability in blood and/or organs, tissues, etc.

The term "thrombosis" will be understood by those skilled in the art to include the formation, development or presence of a thrombus in animals including man, and which may result in embolism and/or ischemia. The term may thus include conditions such as atrophic thrombosis, arterial 5 thrombosis, cardiac thrombosis, coronary thrombosis, creeping thrombosis, infective thrombosis, mesenteric thrombosis, placental thrombosis, propagating thrombosis, traumatic thrombosis and venous thrombosis.

- 10 The term "hypercoagulability" includes any state in which the blood is more readily coagulated than usual.

The term "NVAF" may be understood by those skilled in the art to mean grossly disorganised atrial electrical activity, which is irregular in respect 15 of both rate and rhythm, leading to a hypercoagulable state and an increased risk of thrombosis originating from the left heart chambers, and particularly the left atrium. The term may thus also be understood to include AF (chronic, persistent, permanent and/or intermittent (paroxysmal)) in the absence of heart valvular disease (mostly rheumatic 20 heart valvular disease e.g. mitral stenosis), or prosthesis, and to exclude patients with rheumatic mitral stenosis.

Particular disease states that may be mentioned include the prevention/treatment of ischemic heart disease, myocardial infarction, 25 systemic embolic events in e.g. the kidneys, spleen etc, and, more particularly, of cerebral ischemia, including cerebral thrombosis, cerebral embolism and/or cerebral ischemia associated with non-cerebral thrombosis or embolism (in other words, the treatment/prophylaxis of thrombotic, or ischemic, stroke and of transient ischemic attack (TIA)) in

patients with, or at risk of, NVAF. The skilled person will appreciate that patients with NVAF who are at risk of stroke include elderly patients generally (e.g. those with an age of greater than 75 years); patients with complicating health factors, such as hypertension, left ventricular dysfunction (e.g. left ventricular ejection fraction (LVEF) of less than 40%), symptomatic congestive heart failure, diabetes mellitus (especially in those patients of 65 years of age or greater) and/or coronary heart or artery disease (especially in those patients of 65 years of age or greater); and/or patients with a history of stroke, TIA and/or systemic embolism, all of which factors may predispose such patients to stroke and/or thromboembolic events.

Melagatran, and derivatives thereof, may be administered for systemic delivery using appropriate means of administration that are known to the skilled person.

Thus, in accordance with the invention, melagatran, and derivatives thereof, may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the active ingredient in a pharmaceutically-acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.

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Preferred modes of delivery are systemic. For melagatran, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran, preferred modes of administration are oral.

In the therapeutic treatment of mammals, and especially humans, melagatran and derivatives thereof may be administered alone, but will generally be administered as a pharmaceutical formulation in admixture
5 with a pharmaceutically-acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice.

Suitable formulations for use in administering melagatran and derivatives
10 (including prodrugs) thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912, WO 99/27913, WO 00/12043 and WO 00/13671, the disclosures in which documents are hereby incorporated by
15 reference. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques.

The amount of melagatran or derivative in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as
20 the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

According to a further aspect of the invention there is provided a pharmaceutical formulation for use in the treatment of ischemic disorders
25 in patients having, or at risk of, NVAF comprising an effective amount of melagatran or a pharmaceutically-acceptable derivative thereof in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In the treatment of ischemic disorders, in patients with, or at risk of, NVAF, melagatran and derivatives (including prodrugs) thereof, may also be combined with other agents known for use in the treatment of conditions in which anticoagulant therapy is indicated, for example other
5 thrombin inhibitors, or antithrombotic agents with a different mechanism of action, such as the antiplatelet agents acetylsalicylic acid, ticlopidine, clopidogrel, thromboxane receptor and/or synthetase inhibitors, fibrinogen receptor antagonists, prostacyclin mimetics and phosphodiesterase inhibitors and ADP-receptor (P_2T) antagonists. Melagatran and
10 derivatives (including prodrugs) thereof may also be combined with agents that are known to be useful in the treatment of AF, and particularly NVAF, including known antiarrhythmic agents and heparins.

When melagatran, and derivatives thereof, are "combined" with other
15 therapeutic agents in this way, the active ingredients may be administered together in the same formulation, or administered separately (simultaneously or sequentially) in different formulations.

Suitable doses of melagatran and derivatives thereof, in the therapeutic
20 and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the prior art documents mentioned hereinbefore, the disclosures in which documents are hereby incorporated by reference.

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For example, suitable doses of melagatran, prodrugs and derivatives thereof, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 $\mu\text{mol/L}$, for example in the range 0.001 to 5

μmol/L (e.g. 0.01 to 1 μmol/L, such as 0.05 to 0.5 μmol/L) over the course of treatment of the relevant condition. Suitable doses may thus be in the range 0.1 mg once daily to 25 mg three times daily, and/or up to 100 mg infused parenterally over a 24 hour period, for melagatran, and in 5 the range 0.1 mg once daily to 100 mg three times daily (e.g. 10 to 100 mg twice daily, such as 36 mg twice daily or thereabouts) for prodrugs of melagatran including those specifically mentioned herein.

In any event, the physician, or the skilled person, will be able to 10 determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage 15 ranges are merited, and such are within the scope of this invention.

The skilled person will also appreciate that melagatran, or a derivative thereof, may be administered in an appropriate dose on an "as required" basis (i.e. as needed or desired).

According to a further aspect of the invention there is provided a method 20 of preventing or treating an ischemic disorder in a patient having, or at risk of, NVAF, which comprises administering a therapeutically-effective amount of melagatran, or a pharmaceutically-acceptable derivative thereof, to a patient in need of such treatment.

The use and method described herein may have the advantage that, in the treatment of ischemic disorders in patients with, or at risk of, NVAF, melagatran and derivatives thereof may not possess disadvantages of

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known therapies. The use and method described herein may also have the advantage that melagatran and derivatives thereof may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art for the treatment of ischemic disorders in patients with, or at risk of, NVAF.

The invention is illustrated, but in no way limited, by the following example, in which Figure 1 shows mean plasma concentrations of melagatran with time following administration of particular doses of the prodrug compound EtO₂C-CH₂-(R)Cgl-Aze-Pab-OH.

Example 1

15 Clinical Trial

This was a dose guiding study of Compound "X" (EtO₂C-CH₂-(R)Cgl-Aze-Pab-OH; a prodrug of the active thrombin inhibitor, melagatran; see Example 17 of WO 97/23499) given orally in NVAF. The tolerability of three different doses of X (20, 40, 60 mg p.o. b.i.d.) was compared with 20 warfarin (aiming for an international normalisation ratio (INR) of 2 to 3) over 3 months' treatment in NVAF patients with moderately to high increased risk for stroke or systemic embolic events.

The target enrolment was 220 patients. Eligible patients were newly 25 diagnosed or currently on warfarin or aspirin therapy.

The inclusion criteria for the study were:

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1. History of chronic or intermittent NVAF verified by at least two ECG readings, separated by at least one week. The latest ECG was to be performed at randomisation.
2. In addition to 1 above, at least one of the following risk factors for stroke had to be present:
 - hypertension
 - age \geq 65 years
 - any previous cerebral ischemic attack (stroke or transient ischemic attack [TIA])
 - previous systemic embolism (defined as sudden vascular insufficiency of the limbs or internal organs associated with evidence of arterial occlusion in the absence of previous obstructive disease)
 - left ventricular dysfunction (either left ventricular ejection fraction [LVEF] < 40% or symptomatic congestive heart failure [CHF] within 3 months)
 - diabetes mellitus
 - coronary heart disease
3. Age \geq 18 years. No upper age limit
4. Weight 50 kg to 120 kg (approximately 110 to 265 lb.)

The main exclusion criteria were:

1. Stroke or TIA and/or systemic embolism within the previous 2 years.
2. AF secondary to other reversible disorders, e.g. hyperthyroidosis.
3. Mechanical heart valves.
4. Continuous non-steroidal anti-inflammatory drug (NSAID) treatment.
5. Contraindications for warfarin treatment.
6. Conditions associated with increased risk of bleeding, for example:
 - history of intracranial bleeding

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- history of bleeding gastrointestinal disorder and/or endoscopically-verified ulcer disease within the last year prior to inclusion
 - major surgical procedure or trauma 2 weeks prior to inclusion
 - known hemophilic disorder.
- 5 7. Diastolic blood pressure (DBP) >100 mm Hg or systolic blood pressure (SBP) >180 mm Hg.
8. Renal impairment (calculated creatinine clearance (Calc. CrCl.) < 40 mL/min):

$$\text{Creatinine clearance} = \frac{b \times (140 - \text{age (years)}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/L})}$$

10

(in which b is 1.23 for males, 1.04 for females)

9. Known active liver disease or liver insufficiency.
10. Anemia (Hb < 100 g/L).
11. Platelet count < 100 x 10⁹/L.

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This was a multicentre, multinational, randomized, parallel group, dose-guiding study to compare the safety and tolerability of X with warfarin in stroke prophylaxis in patients with NVAF.

20

Patients were split into four groups: one group receiving 20 mg of X b.i.d., one given 40 (2 x 20) mg of X b.i.d., and one 60 (3 x 20) mg of X b.i.d. The fourth group received warfarin (open label, INR aiming for 2.0 to 3.0). All X medication was given double blind (i.e. neither doctor nor patient knew what tablet strength of X was given).

25

The duration of treatment was 12 weeks. After the 12 week treatment period patients had the option of entering an open label following study on either 40 mg X b.i.d. (if assigned X) or warfarin (if assigned warfarin).

The 40 mg b.i.d. dose was later reduced to 36 mg b.i.d. of X.

ResultsPatient Disposition and Characteristics

- 5 A total of 257 patients were randomized at 32 sites in 11 countries and 254 received at least one dose of study drug. Forty-seven patients (19%) discontinued study drug prematurely and about 167 continued into an open follow-up study (Table 1).

- 10 Table 1 - Patient Disposition

		20mg		40mg		60mg		Warfarin		Total	
Randomised	Yes	66	(100%)	64	(100%)	60	(100%)	67	(100%)	257	(100%)
Rec'd study drug	Yes	66	(100%)	62	(100%)	59	(100%)	67	(100%)	254	(100%)
Prematurely discont.	Yes	10	(15%)	12	(19%)	12	(20%)	13	(19%)	47	(19%)
Cont. into later study	No	18	(27%)	25	(40%)	19	(32%)	24	(36%)	86	(34%)
	Yes	48	(73%)	37	(60%)	40	(68%)	42	(63%)	167	(66%)

- The most frequent reasons for discontinuation are provided in Table 2.
 15 The number of discontinuations and the reasons for discontinuation were evenly distributed among the treatment groups.

Table 2 - Reasons for Treatment Discontinuation

Number of Patients	X Dose			Warfarin
	20 mg	40 mg	60 mg	
Total Discontinued	10	12	12	13
Adverse Event	6	3	5	4
Calc. CrCl <40 mL/min	4	5	4	5
Withdrawn Consent	0	3	2	1
Other	0	1	1	3

Demographic characteristics are shown in Table 3. The patient population
5 was primarily male (61%) and elderly (mean age 69.5, though the age range was 39 to 95) with a mean weight of 83 kg.

Table 3 - Demographics

Parameter	X Dose			Warfarin n=67	TOTAL N=254
	20 mg n=66	40 mg n=62	60 mg n=59		
Average age (years)	69.9	69.7	68.4	70.0	69.5
Age \geq 65 (%)	76	69	69	75	72
Age \geq 75 (%)	26	31	20	31	27
Males (%)	65	68	54	55	61
Weight (kg)	85	85	82	80	83
Calc. CrCl (mL/min)	69	67	69	65	67

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The duration of incidence of NVAF was over 1 year in most patients (73%) and was persistent in almost all (94%) (Table 4). About 80% of patients had between one to three additional risk factors for stroke (75%) with the most common being age \geq 65 (72%), hypertension (57%),
15 coronary heart disease (43%), and left ventricular dysfunction (31%).

Table 4 - AF Characteristics

Parameter	X Dose			Warfarin	TOTAL
	20 mg	40 mg	60 mg		
Duration AF (> 1 year) (%)	74	81	66	71	73
Persistent AF (%)	95	98	93	91	94
Multiple Risk Factors (%)	77	69	80	74	75
Previous Cardioversion Attempt (%)	35	40	31	20	34

- 5 With regard to warfarin management, the percent of patients in the target INR range of 2.0 to 3.0 is displayed by study visit in Table 5. By Visit 7 (week 12) most patients (57%) were in the target range, with 31% having INR values below 2.0 and 12% having values greater than 3.0.

10 Table 5 - Warfarin Management

Visit	Week	N	INR Range		
			1.0-1.9	2.0-3.0	> 3.0
1	0	62	34 (55%)	21 (34%)	7 (11%)
3	1	59	22 (37%)	25 (42%)	12 (20%)
4	2	54	15 (28%)	26 (48%)	13 (24%)
5	4	51	17 (33%)	22 (43%)	12 (24%)
6	8	49	15 (31%)	25 (51%)	9 (18%)
7	12	58	18 (31%)	33 (57%)	7 (12%)

Efficacy Results

- In the warfarin group, two TIAs were reported and in the X group, one ischemic stroke and one TIA were reported (both at 60 mg b.i.d.; see

Table 6. The estimated patient years of observation in the X group (all doses combined) was 40 years for a stroke rate of 2.5% (the annual stroke rate is about 3 to 4% in 65 year old persons not receiving treatment for NVAF, increasing to 10 to 12% in 85 year olds).

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Table 6 - Stroke/TIA Events

Group	Pat.	Gender	Age	CrCl (mLmin)	Stroke/TIA	Prev. stroke	Prev. TIA
60 mg	121	Male	63	78	Ischemic stroke	No	No
	309	Male	65	89	TIA	No	No
Warfarin	120	Male	73	37	TIA	No	No
	153	Female	71	71	TIA	No	No

Safety Results

- 10 The number of unspecified (i.e. not marked as clinically overt on CRF), minor, and major bleeds are shown in Table 7. The only major bleed (genital tract) occurred in the warfarin group. The total number of bleeds and individual bleeding categories were comparable among the treatment groups. There did not appear to be any association between bleeding events and age, creatinine clearance, or gender.
- 15

Table 7 - Bleeding Events

Category	X Dose			Warfarin	Total
	20 mg	40 mg	60 mg		
None	61	57	52	60	230
Unspecified	2	2	4	3	11
Minor	1	0	3	2	6
Multiple Minor	2	3	0	1	6
Major	0	0	0	1	1

The onset pattern of bleeding indicates that most bleeding on the 60 mg b.i.d. dose of X occurs early in the treatment period in a similar pattern to that seen with warfarin.

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Reported adverse events included haematuria, increase in hepatic enzymes, dizziness, pain, diarrhoea, purpura, headache, nausea, fatigue, rash, abdominal pain, haemorrhoids, urinary tract infections, chest pain and vasospasm. The overall frequency of adverse events was low and

10 there were no differences among the treatment groups.

A total of 29 serious adverse events (20 patients) were reported, including one fatal event (pneumonia unrelated to X). There did not appear to be any differences among the groups in the occurrence of non-
15 cerebrovascular serious adverse events.

A few patients treated with X showed asymptomatic increases in liver enzyme levels.

20 Discussion

This study enrolled patients with NVAF and at least one additional risk factors for stroke. Demographic, medical history and AF characteristics were well balanced across the four treatment groups.

25 As expected, very few thromboembolic events (stroke, TIA or systemic emboli) were observed in this study due to the small sample size and short observation period. However, the lack of any excess events in the X groups suggests that X is promising for use in this indication. Only one major bleed was observed in the study (warfarin group) and the

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occurrence of minor bleeds was evenly distributed across all treatment groups.

The lack of increased bleeding at these dose levels suggests a shallow dose response for bleeding and a wide therapeutic index in agreement with animal models.

The pharmacokinetics of X in this population were dose proportional.

- 10 In conclusion, X was well tolerated at doses of up to 60 mg b.i.d. over 3 months. Melagatran and derivatives (including prodrugs) thereof provide promising alternatives to warfarin in the treatment of ischemic disorders in patients with NVAF.
- 15 (Results from ongoing trials, 1 year on from the date of the trial discussed above shows that a 36 mg b.i.d. dose of X (120 treatment years) has resulted in no major bleeds, 2 non-fatal strokes, and 2 TIAs in patients receiving X. In the warfarin group (40 treatment years), 3 major life-threatening bleeds, 2 fatal strokes and 2 TIAs have been reported.)

Claims

1. The use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the manufacture of a medicament for the treatment of an ischemic disorder in a patient having, or at risk of, non-valvular atrial fibrillation.
2. A method of treatment of an ischemic disorder in a patient having, or at risk of, non-valvular atrial fibrillation, which comprises administering a therapeutically effective amount of melagatran, or a pharmaceutically-acceptable derivative thereof, to a patient in need of such treatment.
3. A pharmaceutical formulation for use in the treatment of an ischemic disorder in a patient having, or at risk of, non-valvular atrial fibrillation, which formulation comprises an effective amount of melagatran, or a pharmaceutically-acceptable derivative thereof.
4. Use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the treatment of an ischemic disorder in a patient having, or at risk of, non-valvular atrial fibrillation, by administering melagatran, or a pharmaceutically-acceptable derivative thereof, to a patient.
5. The use of melagatran, or a pharmaceutically-acceptable derivative thereof, in the treatment of an ischemic disorder in a patient having, or at risk of, non-valvular atrial fibrillation.
6. Use, method or formulation as claimed in any one of Claims 1 to 5 (as appropriate), wherein the ischemic disorder to be treated is cerebral ischemia.

7. Use, method or formulation as claimed in Claim 6, wherein the ischemic disorder is thrombotic stroke, ischemic stroke or transient ischemic attack.

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8. Use, method or formulation as claimed in any one of Claims 1 to 7 (as appropriate), wherein the derivative of melagatran is a prodrug of melagatran.

10 9. Use, method or formulation as claimed in Claim 8, wherein the prodrug is of the formula



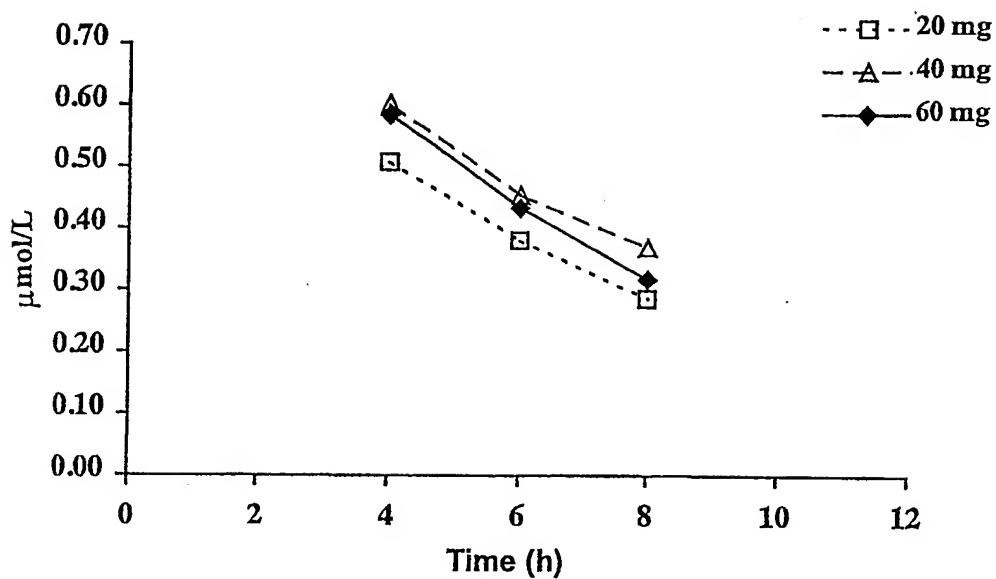
wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab.

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10. Use, method or formulation as claimed in as claimed in Claim 9, wherein R^1 represents methyl, ethyl, *n*-propyl, *i*-propyl or *t*-butyl.

1/1

Figure 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/02204

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/55, A61P 9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA, WPI DATA, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9715190 A1 (MERCH & CO. INC.), 1 May 1997 (01.05.97), page 2, line 20 - line 21 -----	1-10
X	WO 0041716 A1 (ASTRAZENECA AB), 20 July 2000 (20.07.00), see amended claim 4 -----	3

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

22 October 2001

23-10-2001

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02204

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 2, 6-10
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: .
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: .

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORTapplication No.
PCT/SE00/02204

Claims 2, 6-10 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/10/01

International application No.

PCT/SE 00/02204

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9715190 A1	01/05/97	AU	709088 B	19/08/99
		AU	7463496 A	15/05/97
		CA	2233860 A	01/05/97
		EP	0858262 A	19/08/98
		GB	9605163 D	00/00/00
		JP	11514378 T	07/12/99
WO 0041716 A1	20/07/00	AU	2336100 A	01/08/00
		EP	1051590 A	15/11/00
		NO	20013414 D	00/00/00
		SE	9900070 D	00/00/00